A systematic review of the association between umbilical cord characteristics and adverse pregnancy outcomes

Hayes DJL, Warland J, Parast MM, Hasegawa J, Bendon RW & Heazell AEP

Background

- Discussion about umbilical cord abnormalities in 1st Star Legacy Stillbirth Summit in 2011
- Incorporated into STARS Study

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RESEARCH ARTICLE Open Access

An international internet survey of the experiences of 1,714 mothers with a late stillbirth: the STARS cohort study

Jane Warland[1*], Louise M. O'Brien[2], Alexander E. P. Heazell[3], Edwin A. Mitchell[4] and the STARS consortium

Background – STAR Study

1714 women who had experienced stillbirth

1002 were informed of a cause of death (including 593 who were told the cause was unknown).

457 participants (26.7%) were told by their care provider that a cord accident was the cause of their baby's death.

25% of participants believed that a cord abnormality was the cause of their baby's death, but only 312 (68.3 %) who were told that an UCA was CoD agreed with their healthcare provider.

- 32 additional participants included UCA as one of multiple reasons they listed in CoD.
- 23 who were told by their care provider that CoD was a cord issue believed their baby's death was unexplained

Population data

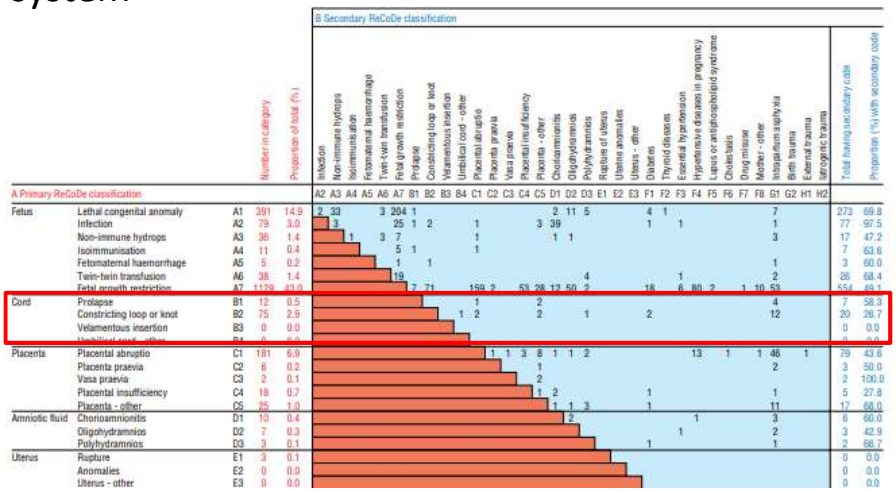
MBRRACE (UK) data from 2016 (CoDAC system)

Table 15: Stillbirths, neonatal deaths, and extended perinatal deaths by CODAC level 1 cause of death: United Kingdom and Crown Dependencies, for births in 2016

CODAC cause of death: level 1	Stillbirths[§]		Neonatal deaths[§]		Extended perinatal deaths[§]	
	Number	%	Number	%	Number	%
Infection	108	3.5	101	7.6	209	4.7
Neonatal	42	1.4	586	43.8	628	14.3
Intrapartum	71	2.3	27	2.0	98	2.2
Congenital anomaly	280	9.1	448	33.5	728	16.5
Fetal	149	4.9	49	3.7	198	4.5
Cord	130	4.2	2	0.1	132	3.0
Placenta	882	28.8	31	2.3	913	20.7
Maternal	122	4.0	5	0.4	127	2.9
Unknown	1145	37.4	65	4.9	1210	27.5
Missing	136	4.4	23	1.7	159	3.6

[§] excluding terminations of pregnancy and births <24+0 weeks gestational age
Data source: MBRRACE-UK

Gardosi et al. BMJ 2005, ReCoDe classification system



A Primary ReCoDe classification			Number in category	Proportion of total (%)	B Secondary ReCoDe classification: A2 Infection	A3 Non-immune hydrops	A4 Isoimmunisation	A5 Fetomaternal haemorrhage	A6 Twin-twin transfusion	A7 Fetal growth restriction	B1 Prolapse	B2 Constricting loop or knot	B3 Velamentous insertion	B4 Umbilical cord - other	C1 Placental abruptio	C2 Placenta praevia	C3 Vasa praevia	C4 Placental insufficiency	C5 Placenta - other	D1 Chorioamnionitis	D2 Oligohydramnios	D3 Polyhydramnios	E1 Rupture of uterus	E2 Uterine anomalies	E3 Uterus - other	F1 Diabetes	F2 Thyroid diseases	F3 Essential hypertension	F4 Hypertensive diseases in pregnancy	F5 Lupus or antiphospholipid syndrome	F6 Cholestasis	F7 Drug misuse	F8 Mother - other	G1 Iatrogenic/planned/elective	G2 Birth trauma	H1 External trauma	H2 Iatrogenic trauma	Total having secondary code	Proportion (%) with secondary code
Fetus	Lethal congenital anomaly	A1	391	14.9	2	33			3	204	1								2	11	5			4	1							7					273	69.8
	Infection	A2	79	3.0	3				25	1	2			1				3	39					1		1					1					77	97.5
	Non-immune hydrops	A3	36	1.4		1		3	7					1					1	1											3					17	47.2
	Isoimmunisation	A4	11	0.4					5	1				1																						7	63.6
	Fetomaternal haemorrhage	A5	5	0.2					1		1																				1					3	60.0
	Twin-twin transfusion	A6	38	1.4					19													4					1				2					26	68.4
	Fetal growth restriction	A7	1128	43.0						7	71			159	2		53	28	12	50	2			18		6	80	2		1	10	53					554	49.1
Cord	Prolapse	B1	12	0.5										1				2													4					7	58.3
	Constricting loop or knot	B2	75	2.9								1	2					2			1			2							12					20	26.7
	Velamentous insertion	B3	0	0.0																																0	0.0
	Umbilical cord - other	B4	0	0.0																																0	0.0
Placenta	Placental abruptio	C1	181	6.9											1	1	3	8	1	1	2							13	1	1	46	1				79	43.6
	Placenta praevia	C2	6	0.2														1													2					3	50.0
	Vasa praevia	C3	2	0.1														2																			2	100.0
	Placental insufficiency	C4	18	0.7														1	2					1							1						5	27.8
	Placenta - other	C5	25	1.0															1	1	3			1							11					17	68.0
Amniotic fluid	Chorioamnionitis	D1	10	0.4																2							1				3					6	60.0
	Oligohydramnios	D2	7	0.3																						1					2					3	42.9
	Polyhydramnios	D3	3	0.1																				1							1					2	66.7
Uterus	Rupture	E1	3	0.1																																0	0.0
	Anomalies	E2	0	0.0																																0	0.0
	Uterus - other	E3	0	0.0																																0	0.0

Summary

- Large variability in different estimates of association between cord abnormalities and stillbirth
- Feeds uncertainty for parents about cause of their child's stillbirth
- Systematic review and meta-analysis gives opportunity to assemble and pool all data; improves accuracy of estimate and understand variation

Aims of systematic review

- What are the normal characteristics of human umbilical cord?
- How frequently are abnormalities of the umbilical cord present?
- Are abnormalities of the umbilical cord associated with stillbirth and other adverse pregnancy outcomes?
- Which abnormalities of the umbilical cord are associated with stillbirth and other adverse pregnancy outcomes?

Methods

- Systematic literature searches were constructed with the aim of finding all relevant published studies since 1960

- MEDLINE, EMBASE, CINAHL, and Google Scholar were searched. Additionally, reference lists of relevant studies, conference proceedings, and book chapters were searched as well as unpublished literature

Inclusion criteria:

Studies of umbilical cord abnormalities in singleton pregnancies after 20 weeks of gestation

Study types:

- Cohort or cross-sectional studies that report normal characteristics of umbilical cord or the incidence of abnormalities
- Cohort studies that report the incidence of abnormalities and their relation to adverse pregnancy outcomes
- Case control studies of pregnancies with and without cord abnormalities

Main outcome:

Stillbirth (death of a baby before birth and after 20 weeks' gestation)

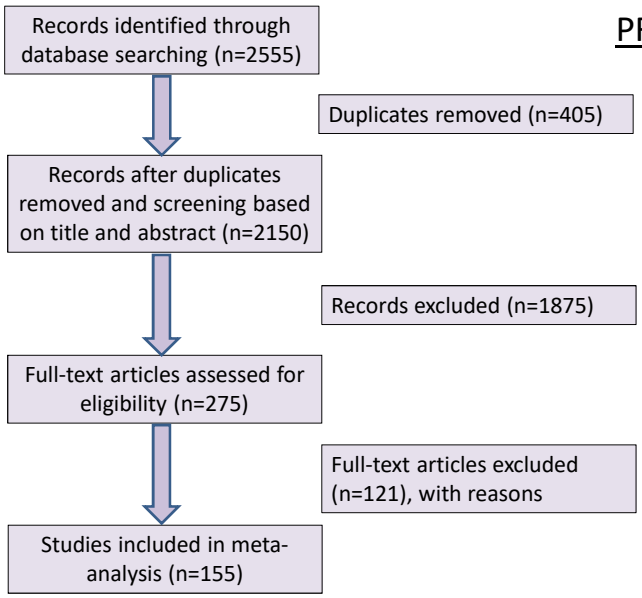
Additional outcomes:

NICU admission, preterm delivery (<37 weeks), small for gestational age (SGA; BW <10th centile or as defined by study), low birth weight (<2500g), low Apgar score (<7 at 5 minutes or 1 minute)

UCA:

Nuchal cord (cord wrapped around the neck of the baby); true knot (knotted cord); cord prolapse (the cord descends from the uterus before the baby); hyper/hypocoiling (over or undercoiling of the cord)

PRISMA diagram



Study aims

- **What are the normal characteristics of human umbilical cord?**
- How frequently are abnormalities of the umbilical cord present?
- Are abnormalities of the umbilical cord associated with stillbirth and other adverse pregnancy outcomes?
- Which abnormalities of the umbilical cord are associated with stillbirth and other adverse pregnancy outcomes?

Results - cord length

- We found **39 studies of 94,869 pregnancies** that presented data for average cord length at birth. Using these, we calculated an overall average length of **584mm** (±253mm).
- Included studies of cord length used varying definitions; 'short cord' ranged from <350mm to <500mm, 'long cord from >590mm to >950mm.
- Due to a lack of studies with data for the same outcomes at the same thresholds, we could not investigate the relationship between cord length and adverse outcomes.

Results - coiling

- We found the average umbilical coiling index (UCI) at delivery to be **0.22 ± 0.10**, data were taken from 17 studies of 7371 pregnancies
- In the majority of studies, hypercoiling and hypocoiling were defined as above the 90th and below the 10th centiles respectively so the incidences are 10% by default

Study aims

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- Are abnormalities of the umbilical cord associated with stillbirth and other adverse pregnancy outcomes?
- Which abnormalities of the umbilical cord are associated with stillbirth and other adverse pregnancy outcomes?

Incidence of cord abnormalities

Cord abnormality	Incidence	95% CI	Number of studies	Number of pregnancies
Nuchal cord at delivery (all)	22%	19 to 25%	50	694,681
Single loop at delivery	16%	13 to 20%	28	81,138
Multiple loops at delivery	4%	3 to 5%	28	102,970
Nuchal cord using ultrasound	27%	20 to 35%	14	4,191
True knot at delivery	1%	0 to 1%	25	1,279,949
Cord prolapse	6%	0 to 12%	21	11,057,165

Hyper and hypocoiling were defined as above the 90th and below the 10th centiles so incidence was 10% by definition.
We found four studies that recorded the incidence of other entanglements (limbs, trunk) separately, incidences ranged from 0.2 to 3%.

Study aims

- What are the normal characteristics of human umbilical cord?
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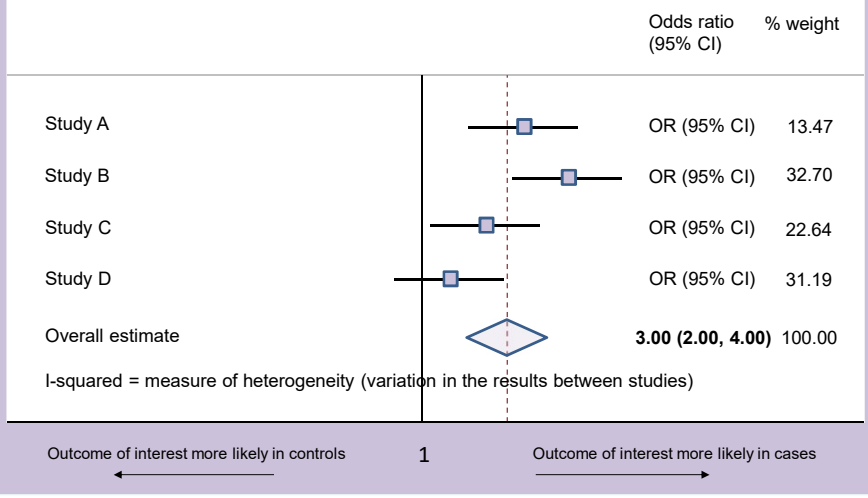
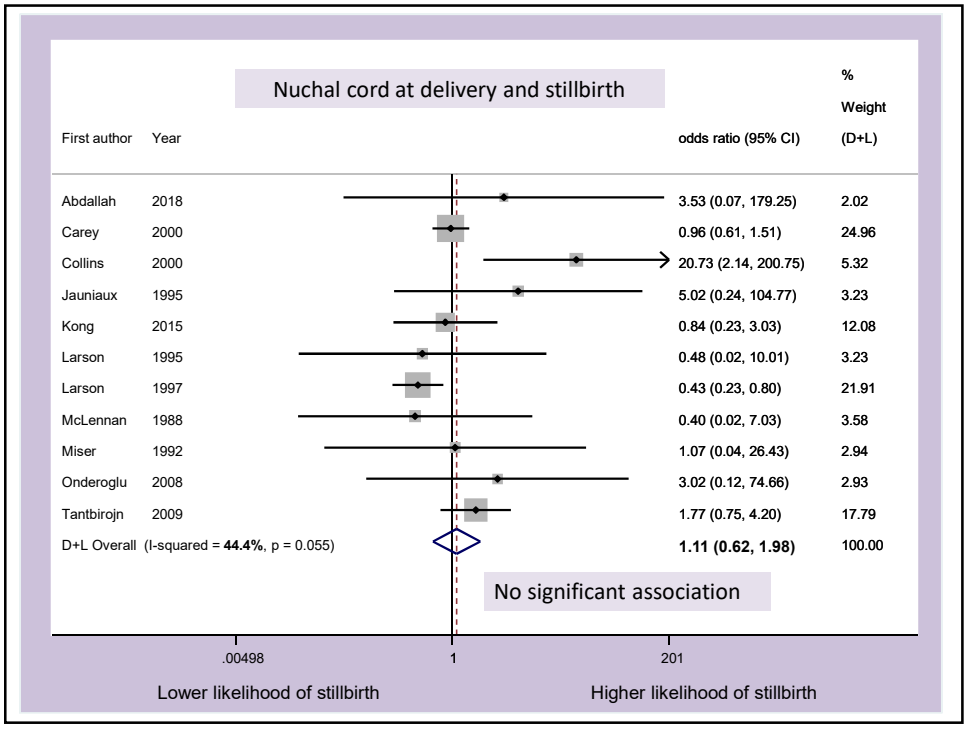
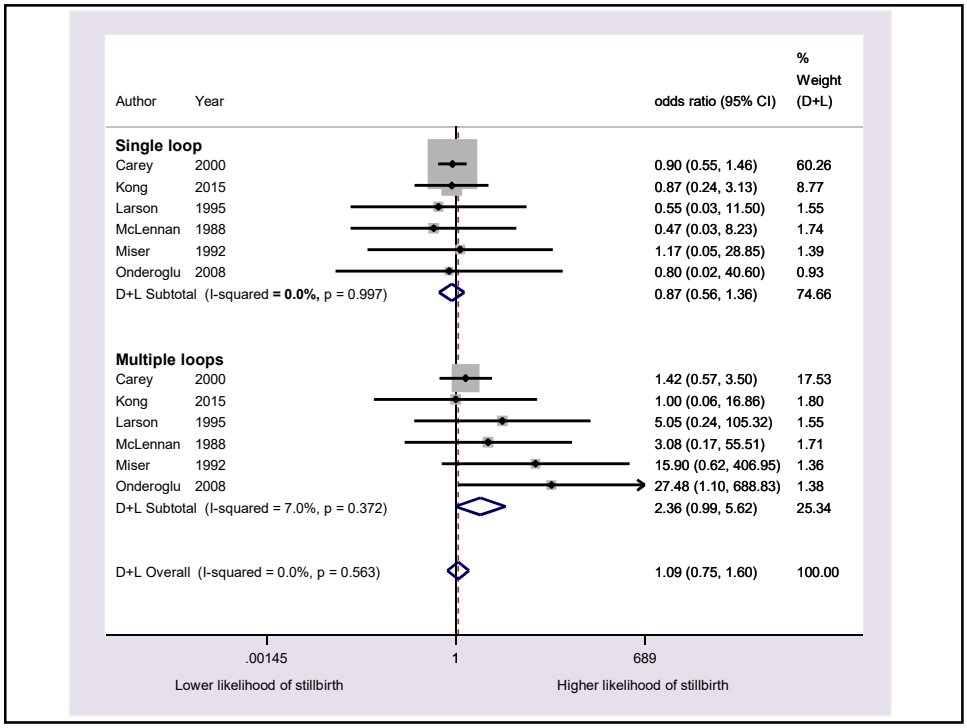
- **Which abnormalities of the umbilical cord are associated with stillbirth and other adverse pregnancy outcomes?**

Forest plots




Nuchal cord at delivery and stillbirth
First author
Year
odds ratio (95% CI)
% Weight (D+L)
Abdallah 2018 3.53 (0.07, 179.25) 2.02
Carey 2000 0.96 (0.61, 1.51) 24.96
Collins 2000 20.73 (2.14, 200.75) 5.32
Jauniaux 1995 5.02 (0.24, 104.77) 3.23
Kong 2015 0.84 (0.23, 3.03) 12.08
Larson 1995 0.48 (0.02, 10.01) 3.23
Larson 1997 0.43 (0.23, 0.80) 21.91
McLennan 1988 0.40 (0.02, 7.03) 3.58
Miser 1992 1.07 (0.04, 26.43) 2.94
Onderoglu 2008 3.02 (0.12, 74.66) 2.93
Tantbirojn 2009 1.77 (0.75, 4.20) 17.79
D+L Overall (I-squared = 44.4%, p = 0.055) 1.11 (0.62, 1.98) 100.00
No significant association
.00498
1
201
Lower likelihood of stillbirth
Higher likelihood of stillbirth


Author
Year
odds ratio (95% CI)
% Weight (D+L)
Single loop
Carey 2000 0.90 (0.55, 1.46) 60.26
Kong 2015 0.87 (0.24, 3.13) 8.77
Larson 1995 0.55 (0.03, 11.50) 1.55
McLennan 1988 0.47 (0.03, 8.23) 1.74
Miser 1992 1.17 (0.05, 28.85) 1.39
Onderoglu 2008 0.80 (0.02, 40.60) 0.93
D+L Subtotal (I-squared = 0.0%, p = 0.997) 0.87 (0.56, 1.36) 74.66
Multiple loops
Carey 2000 1.42 (0.57, 3.50) 17.53
Kong 2015 1.00 (0.06, 16.86) 1.80
Larson 1995 5.05 (0.24, 105.32) 1.55
McLennan 1988 3.08 (0.17, 55.51) 1.71
Miser 1992 15.90 (0.62, 406.95) 1.36
Onderoglu 2008 27.48 (1.10, 688.83) 1.38
D+L Subtotal (I-squared = 7.0%, p = 0.372) 2.36 (0.99, 5.62) 25.34
D+L Overall (I-squared = 0.0%, p = 0.563) 1.09 (0.75, 1.60) 100.00
.00145
1
689
Lower likelihood of stillbirth
Higher likelihood of stillbirth

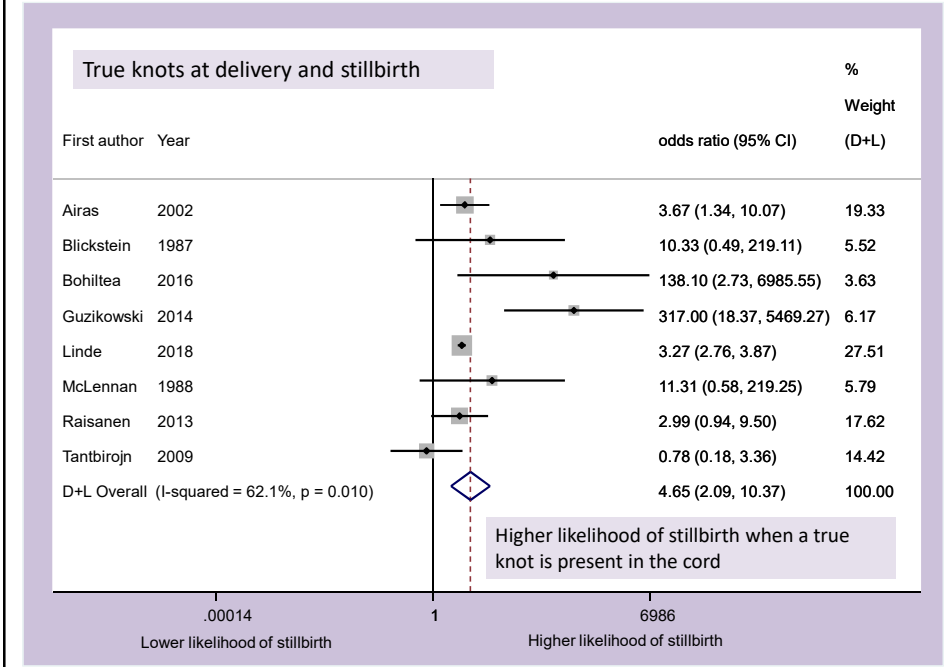
Nuchal cord in relation to adverse pregnancy outcomes

	Stillbirth	CS	1 min Apgar score <7	5 min Apgar score <7	NICU admission
All nuchal cords	1.11 (0.62 to 1.98)	1.10 (0.91 to 1.33)	**1.81 (1.38 to 2.36)**	1.18 (0.90 to 1.54)	1.15 (0.99 to 1.34)
Single loop	0.87 (0.56 to 1.35)	0.66 (0.50 to 0.88)	**1.80 (1.22 to 2.65)**	0.86 (0.42 to 1.75)	1.01 (0.86 to 1.18)
Multiple loop (single loop plus no NC as controls)	1.91 (0.90 to 4.06)	**1.60 (1.10 to 2.32)**	**3.39 (2.30 to 5.01)**	**2.74 (1.12 to 6.73)**	1.75 (0.92 to 3.34)
Multiple loop (no NC as controls)	2.36 (0.99 to 5.62)	**1.66 (1.21 to 2.28)**	**2.77 (1.53 to 5.03)**	2.20 (0.75 to 6.48)	1.79 (0.92 to 3.49)
Tight loop (no NC as controls)	Not enough data	1.28 (0.33 to 4.94)	**10.61 (4.53 to 24.82)**	**7.70 (2.28 to 25.97)**	3.20 (0.87 to 11.77)
Loose loop (no NC as controls)	Not enough data	0.58 (0.31 to 1.07)	0.93 (0.42 to 2.05)	0.65 (0.13 to 3.18)	0.91 (0.48 to 1.71)

Other analyses – nuchal cord

- No associations were found between nuchal cord at delivery and birth weight (as IUGR, SGA, LBW), we did not have enough data to look at preterm delivery (two studies)

- Not enough data to look at the association between nuchal cord detected antenatally and adverse outcomes, except for caesarean section which was more likely (OR 1.64, 95% CI 1.07 to 2.51; 2307 pregnancies from four studies)

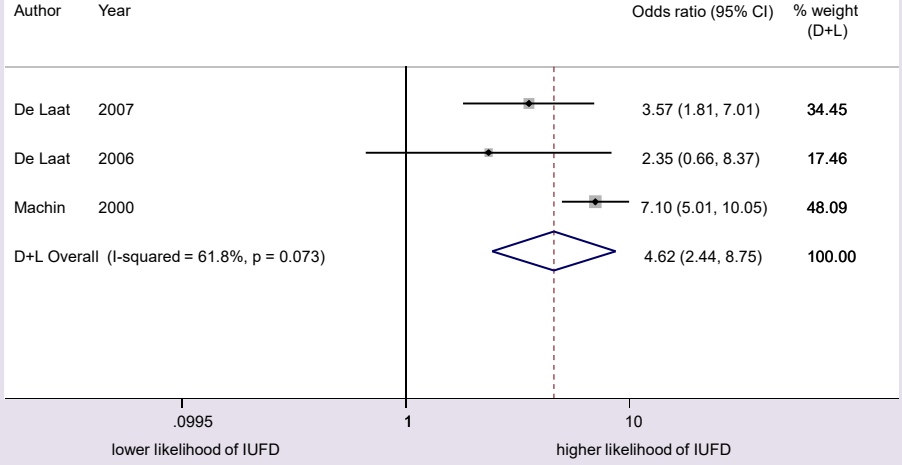


True knots and adverse pregnancy outcomes

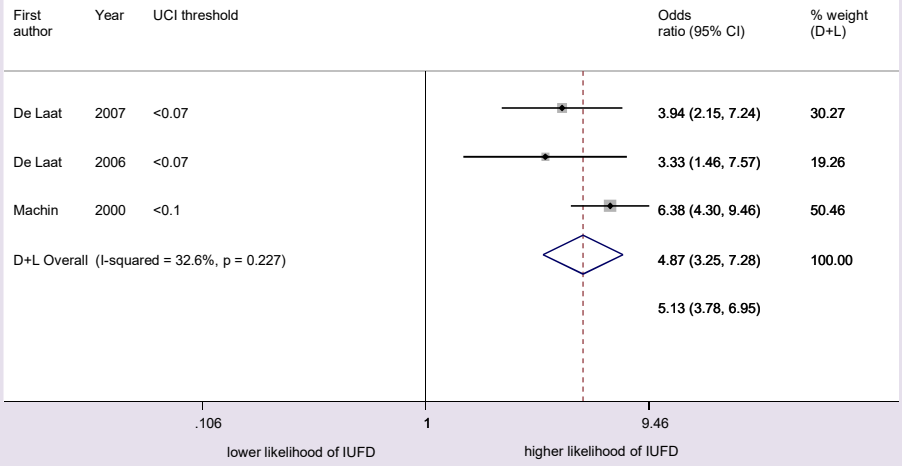
	Stillbirth	CS	PTD (<37 weeks)	5 min Apgar score <7	NICU admission
Odds ratio (95% CI)	**4.65 (2.09 to 10.37)**	1.22 (0.95 to 1.55)	**1.15 (1.05 to 1.25)**	**1.56 (1.15 to 2.11)**	**1.24 (1.16 to 1.32)**
I^2 (% of variation due to heterogeneity)	60.0% (p<0.05)	71.6% (p<0.005)	1.6% (p=0.362)	36.9% (p=0.191)	1.8% (p=0.361)
Number of pregnancies (no. of knots)	911,814 (12,001)	977,290 (12,779)	907,024 (11,897)	908,040 (11,953)	907,152 (11,899)
Notes	All knots detected at delivery	Mixture of EmCS and all CS; knots never an indication for CS	Three studies, one 92.27% of weight		Three studies, one 92.27% of weight

Two studies presented data for 1 min Apgar score <7. Data were not sufficient to look at the association between multiple knots and adverse outcomes.

Hypercoiling (>0.3 UCI) and IUFD



Hypocoiling and IUFD



Abnormal coiling and adverse pregnancy outcomes

	IUFD	Apgar <7 at 5 min	LBW (<2500g)	PTD (<37w)	CS
Hypercoiling	4.62 (2.44 to 8.75)	2.37 (0.98 to 5.71)	4.98 (1.61 to 15.37)	1.63 (1.28 to 2.09)	2.74 (1.11, 6.78)
Notes	>0.3 UCI at delivery	All definitions combined, coiling measured after delivery			
Hypocoiling	4.87 (3.25 to 7.28)	5.55 (2.21 to 13.90)	3.02 (1.65 to 5.51)	2.17 (1.49 to 3.15)	1.73 (1.25, 2.40)
Notes	<0.1 UCI at delivery	All definitions combined, coiling measured after delivery			

Three studies measured NICU admission, one had zero admissions in either coiling group.

Conclusions

- **Nuchal cord** is present at delivery in 22% of all pregnancies but its relationship to stillbirth is still unclear. There may be a trend towards increased likelihood with multiple loops, we were not able to analyse if cord tightness has an effect.
- A single loop of cord is associated with low 1 minute Apgar scores; multiple loops are associated with increased likelihood of Caesarean section and low Apgar scores at 1 & 5 minutes. Tight loops of cord were also associated with low Apgar scores.

Conclusions

- A **true knot** of the umbilical cord is a rare event but one that is linked to a 4x increase in the likelihood of stillbirth when compared to a cord that is not knotted
- Other adverse outcomes (preterm delivery, low Apgar scores, NICU admission) are also significantly more likely with cord knots but the effect sizes are much smaller (between 1.15 and 1.56)

Conclusions

- Our data show that **abnormal coiling** may be linked to significantly increased likelihood of IUFD, low Apgar scores, preterm delivery, low birth weight, and caesarean section.
- However, data were only from a few studies for some outcomes, mixed thresholds were used, and some studies included significant percentages of placentas that were referred to pathology.
- More studies are needed to confirm these effects but our results agree with another recent systematic review (Pergialiotis et al. 2019)

Limitations

Nuchal cord and stillbirth

- We could not look at effects on antepartum and intrapartum stillbirth separately
- Not all studies recorded number or tightness of loops; no studies recorded type A or B nuchal cord
- Individual studies were not adequately powered to detect differences in stillbirth (in total we only analysed 117 stillbirths; 24 with single loops of cord and 6 with multiple nuchal cords)

Limitations

- We were not able to investigate the effects of multiple UCA together and could not look at the effect of cord length on adverse outcomes.
- Cord abnormalities were often defined differently by different studies.
- We were not able to look at the effect of gestation for most of our outcomes.
- There may be other confounding factors at play that we could not measure.

Recommendations for future studies

- Adequately powered prospective studies of the relationship between UCA and pregnancy outcomes are needed, with details of all UCA recorded both antenatally and after delivery.
- Nuchal cord in particular is an area that needs much larger prospective studies complete with far more stringent monitoring and recording of the condition.

Acknowledgements

- Star Legacy Foundation for funding the work
- Alex, Mana, Jane, Bob, Junichi
- Julia Banks and Laura Clapham for additional help with data extraction
- Translators

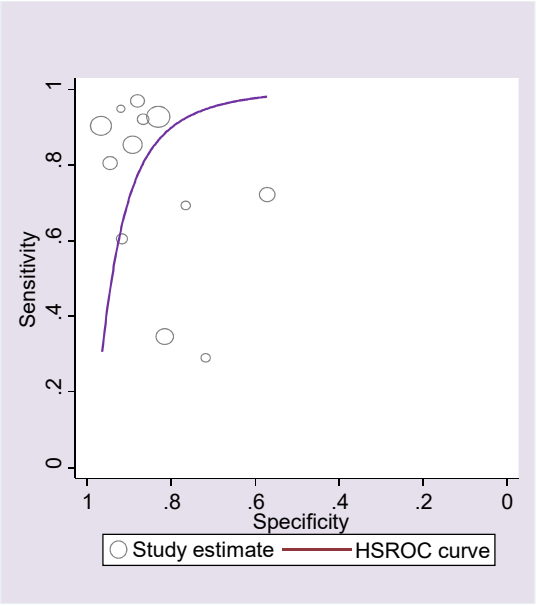
Thank you for listening!

- any questions?

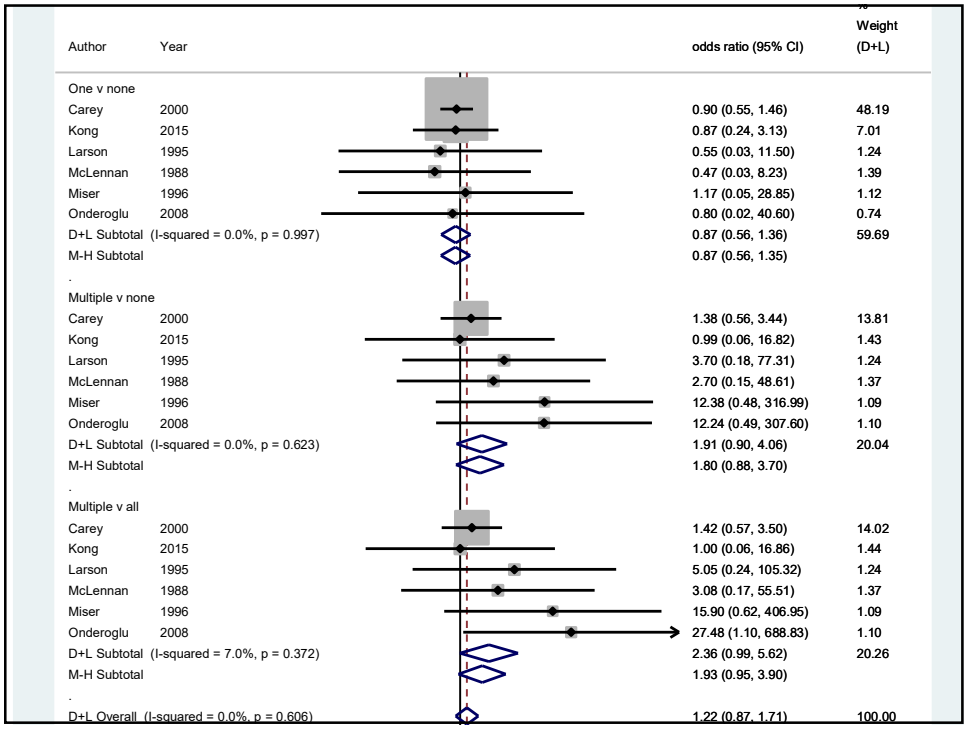
STAR LEGACY FOUNDATION

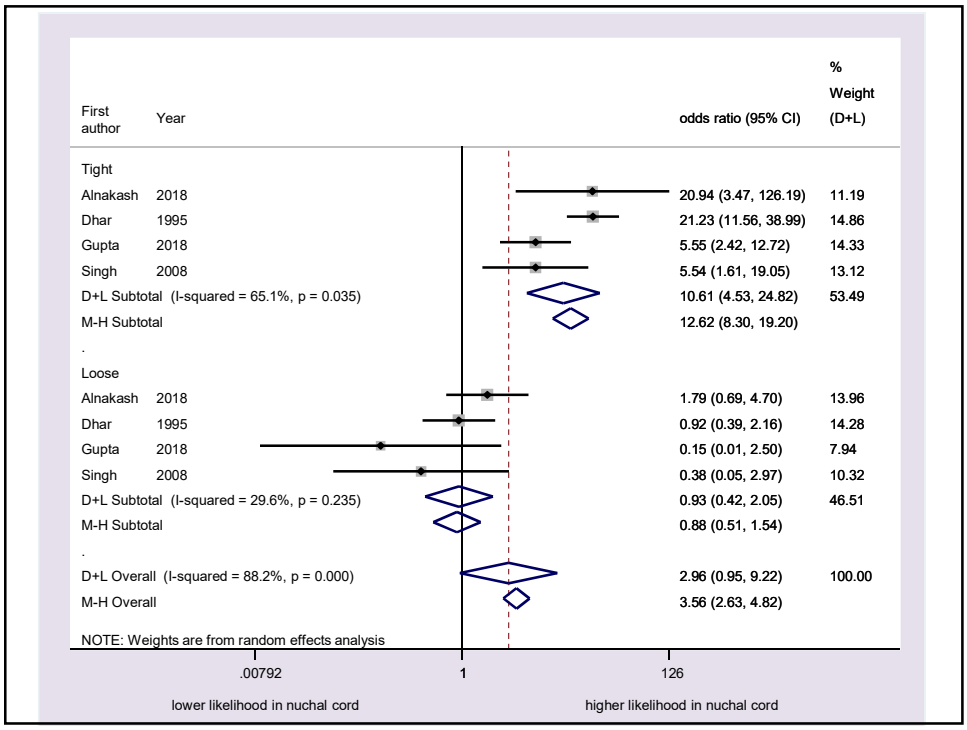
Diagnostic accuracy of ultrasound for detecting nuchal cords antenatally

- Data from 12 studies
- Summary sensitivity 80.5%, specificity 86.6%
- No trend towards higher accuracy with measurements closer to term although three studies performed ultrasound in active labour and all had sensitivities above 90%, specificities above 83%.



	Stillbirth	CS	1 min Apgar score <7	5 min Apgar score <7	NICU admission
All nuchal cords	40,011 (11 studies)	270,973 (24 studies)	195,424 pregnancies (16 studies)	209,321 pregnancies (17 studies)	243,226 pregnancies (12 studies)
Single loop	28,687 (six studies)	31,230 (seven studies)	17,568 pregnancies (four studies)	29,718 pregnancies (six studies)	21,097 pregnancies (five studies)
Multiple loop (single loop plus no NC as controls)	29,629 (six studies)	32,851 (seven studies)	17,906 pregnancies (four studies)	34,764 pregnancies (seven studies)	22,332 pregnancies (five studies)
Multiple loop (no NC as controls)	22,649 (six studies)	25,028 (seven studies)	14,100 pregnancies (five studies)	26,638 pregnancies (six studies)	16,824 pregnancies (five studies)
Tight loop (no NC as controls)	Not enough data	61,044 (seven studies)	1485 pregnancies (four studies)	985 pregnancies (three studies)	172,656 pregnancies (three studies)
Loose loop (no NC as controls)	Not enough data	3,255 (six studies)	1649 pregnancies (four studies)	1111 pregnancies (three studies)	205,634 pregnancies (three studies)


Author
Year
odds ratio (95% CI)
% Weight (D+L)
One v none
Carey 2000 0.90 (0.55, 1.46) 48.19
Kong 2015 0.87 (0.24, 3.13) 7.01
Larson 1995 0.55 (0.03, 11.50) 1.24
McLennan 1988 0.47 (0.03, 8.23) 1.39
Miser 1996 1.17 (0.05, 28.85) 1.12
Onderoglu 2008 0.80 (0.02, 40.60) 0.74
D+L Subtotal (I-squared = 0.0%, p = 0.997) 0.87 (0.56, 1.36) 59.69
M-H Subtotal 0.87 (0.56, 1.35)
Multiple v none
Carey 2000 1.38 (0.56, 3.44) 13.81
Kong 2015 0.99 (0.06, 16.82) 1.43
Larson 1995 3.70 (0.18, 77.31) 1.24
McLennan 1988 2.70 (0.15, 48.61) 1.37
Miser 1996 12.38 (0.48, 316.99) 1.09
Onderoglu 2008 12.24 (0.49, 307.60) 1.10
D+L Subtotal (I-squared = 0.0%, p = 0.623) 1.91 (0.90, 4.06) 20.04
M-H Subtotal 1.80 (0.88, 3.70)
Multiple v all
Carey 2000 1.42 (0.57, 3.50) 14.02
Kong 2015 1.00 (0.06, 16.86) 1.44
Larson 1995 5.05 (0.24, 105.32) 1.24
McLennan 1988 3.08 (0.17, 55.51) 1.37
Miser 1996 15.90 (0.62, 406.95) 1.09
Onderoglu 2008 27.48 (1.10, 688.83) 1.10
D+L Subtotal (I-squared = 7.0%, p = 0.372) 2.36 (0.99, 5.62) 20.26
M-H Subtotal 1.93 (0.95, 3.90)
D+L Overall (I-squared = 0.0%, p = 0.606) 1.22 (0.87, 1.71) 100.00


First author
Year
odds ratio (95% CI)
% Weight (D+L)
Tight
Alnakash 2018 20.94 (3.47, 126.19) 11.19
Dhar 1995 21.23 (11.56, 38.99) 14.86
Gupta 2018 5.55 (2.42, 12.72) 14.33
Singh 2008 5.54 (1.61, 19.05) 13.12
D+L Subtotal (I-squared = 65.1%, p = 0.035) 10.61 (4.53, 24.82) 53.49
M-H Subtotal 12.62 (8.30, 19.20)
Loose
Alnakash 2018 1.79 (0.69, 4.70) 13.96
Dhar 1995 0.92 (0.39, 2.16) 14.28
Gupta 2018 0.15 (0.01, 2.50) 7.94
Singh 2008 0.38 (0.05, 2.97) 10.32
D+L Subtotal (I-squared = 29.6%, p = 0.235) 0.93 (0.42, 2.05) 46.51
M-H Subtotal 0.88 (0.51, 1.54)
D+L Overall (I-squared = 88.2%, p = 0.000) 2.96 (0.95, 9.22) 100.00
M-H Overall 3.56 (2.63, 4.82)
NOTE: Weights are from random effects analysis
.00792
1
126
lower likelihood in nuchal cord
higher likelihood in nuchal cord

Results - quality assessment

- Quality of included studies was mostly judged to be fair (studies could be classified as *good*, *fair*, or *poor*)
- Most studies had issues with: sample size justifications, measuring different levels of exposures, definitions of exposures and/or outcome measures, blinding of exposure assessors.
- Sensitivity analyses were performed where studies rated *poor* were removed to test if they had an effect on our results

Systematic Review of Cord Characteristics – Vasa Praevia

- 13 studies of 569 410 patients; 325 cases of VP.
- 10 included cohort studies providing information on the incidence - 0.60 per 1000 pregnancies
- ~83% of the cases of VP had one or more factors

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Systematic review

Incidence of and risk indicators for vasa praevia: a systematic review

L Ruiter,[a] N Kok,[b] J Limpens,[c] JB Derks,[d] IM de Graaf,[a] BWJ Mol,[e] E Pajkrt[a]

[a] Department of Obstetrics and Gynaecology, Academic Medical Centre Amsterdam, Amsterdam, the Netherlands [b] Department of Obstetrics and Gynaecology, Vrije Universiteit Medical Centre, Amsterdam, the Netherlands [c] Medical Library, Academic Medical Centre, Amsterdam, the Netherlands [d] Department of Obstetrics and Gynaecology, University Medical Centre, Utrecht, the Netherlands [e] The Robinson Institute, School of Paediatrics and Reproductive Health, University of Adelaide, Adelaide, SA, Australia

Correspondence: L Ruiter, Academic Medical Centre, Department of Obstetrics and Gynecology, H4-240, Post box 226000, 1100DD Amsterdam, the Netherlands. Email l.ruiter@amc.nl

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